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Breast Cancer

Triple-Negative Breast Cancer in Lebanon: A Case Series

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ABSTRACT

Objectives. **To determine the incidence, characteristics, and survival outcomes of triple-negative breast cancer patients in a medical oncology practice in Lebanon.**

Methods. **The pathology reports of all breast cancer cases diagnosed or treated in 1997–2008 were reviewed.**

Results. **One hundred seventy breast cancer cases (9.3%) of the 1,834 cases that were identified in this practice over a 10-year span had a triple-negative phenotype, with a median age at diagnosis of 52 years. The pathology distribution of those cases was as follows: invasive ductal carcinoma, 85%; medullary carcinoma, 5%; invasive lobular carcinoma, 5%; 95 cases (63%) were grade III. At diagnosis, 17% presented with stage I, 47% had stage II, 24% had stage III, and 12% had stage IV disease, whereas 11% had an inflammatory component. After a median follow-up of 17 months, 43 patients (25.3%) had relapsed and the most common sites of relapse were the brain (19%), lungs (19%), and bones (12%). The risk for recurrence peaked at 1.5 years and became almost nil after 3 years. Twenty patients received induction chemotherapy, among whom six (42.9%) had a complete response and six (42.9%) had a partial response to treatment. None of the patients progressed on neoadjuvant chemotherapy. The 5-year disease-free survival rate was 75% for stage I, 58% for stage II, and 40% for stage III patients, whereas the 5-year overall survival rate was 88% for stage I, 72% for stage II, and 63% for stage III patients. Adjuvant therapy was administered to 96% of patients, using a taxane-based regimen in 38% of cases. The median survival time for stage IV patients was 19 months, with a first line taxane-based regimen used in 50% of cases.**

Conclusions. **The incidence of triple-negative breast cancer in Lebanon is similar to that described in the literature. In order to determine targets for future therapeutic options, it is essential to understand the biology of this particular breast cancer subtype.** ***The Oncologist*** 2011;16: 1552–1556

INTRODUCTION

Breast cancer is the most common malignancy in women in Lebanon, because, according to the Lebanese Ministry of Health, there are 1,751 new cases per year [1].

In an article entitled "Molecular portraits of human breast tumors," Perou et al. [2] defined four new subtypes of breast cancer: luminal A, B, and C; normal breast-like; Human epidermal growth factor receptor (HER)-2^+, and basal-like. The estrogen receptor (ER), progesterone receptor (PgR), and HER-2/neu triple-negative phenotype is associated with a higher likelihood of recurrence and death [3]. Triple-negative breast cancers account for approximately 10%–17% of all breast cancers [4], are more frequent in black and premenopausal women [5, 6], and are known to be rapidly growing cancers because they can emerge between two normally timed mammographies [7]. When diagnosed, triple-negative breast cancers are often locally advanced and of high grade; however, little relationship has been established between the size of the tumor and lymph node involvement [3]. The most frequent sites of metastasis are the lungs and brain [8]. The risk for re-

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currence for this very particular subtype of cancer is elevated during the few months following diagnosis, with a peak at 1–2 years, and is null after 8 years. The highest mortality risk occurs during the first 5 years after diagnosis [3]. Paradoxically, triple-negative breast cancers show a strong clinical response to neoadjuvant chemotherapy [9]. Ongoing trials aim to evaluate new targeted therapies for this subtype of cancer [10].

Materials and Methods

The purpose of this study was to determine the incidence, characteristics, and survival outcomes of triple-negative breast cancer patients in a medical oncology practice that encompasses five oncologists. The pathology of all breast cancer cases diagnosed or treated in 1997–2008 was retrospectively reviewed. We included in our study only adult patients aged >18 years diagnosed with breast cancer anytime between January 1997 and January 2008 whose pathology report was available with an ER expression rate <10% on immunohistochemistry (IHC), a PgR expression rate <10% on IHC, and no HER-2 expression on IHC or HER-2 1+ or 2+ expression on IHC accompanied by a negative fluorescence in situ hybridization (FISH) result.

Our study excluded patients whose pathology report was unavailable, patients not tested for HER-2 expression by IHC, and patients whose HER-2 status was 2+ on IHC but for whom FISH was not done. In total, 201 patients were excluded from the study. Ninety percent of the pathology reports were reviewed at Hotel-Dieu de France and Institut National de Pathologie, both of which have highly reliable pathology departments. Breast cancer staging was done using the sixth edition of the American Joint Committee on Cancer Cancer Staging Manual. The tumor size and its possible extension to the chest wall as well as the number of positive lymph nodes were defined using a baseline mammography and additional imaging studies including computed tomography and positron emission tomography. Lymph node staging was based on imaging for patients who had received neoadjuvant chemotherapy and on the pathology report for those who were directly sent to surgery.

Metastases were looked for in symptomatic patients, using magnetic resonance imaging of the brain, bone scintigraphy, computed tomography, and liver ultrasound. The response to neoadjuvant chemotherapy was clinical and followed the Response Evaluation Criteria in Solid Tumors.

For our statistical analysis, the overall survival rate was calculated according to the time of diagnosis and death or the last contact with the patient. Survival curves were drawn according to Kaplan–Meier survival estimates and the log-rank test. A p-value $<.05$ was considered of statistical significance.

Results

One hundred seventy breast cancer cases (9.3%) of the 1,834 cases that were identified in this practice over a 10-year span had the triple-negative phenotype, with a median age at diagnosis of 52 years. A positive family history of breast/ovarian cancer was found in 15 (9%) triple-negative breast cancer patients, with a relationship of second and third degree. The pathology distribution of those cases was as follows: invasive ductal carcinoma, 85%; medullary carcinoma, 5%; invasive lobular carcinoma, 5%; mucinous carcinoma, 2%; and epidermoid carcinoma, 0.6%.

The majority of tumors were poorly differentiated. Ninety-five cases (63%) were grade III and presented with a high index of proliferation, with a mean Ki-67 index of ~49%. Specific markers for basal-like tumors are not routinely looked for in our center. Approximately half of the tumors were T2 lesions, whereas T4 lesions were present in 11.9% of cases. More than half of the patients had positive lymph nodes at diagnosis and only 13% had metastasis. At presentation, 17% had stage I, 47% had stage II, 24% had stage III, and 12% had stage IV disease, whereas 11% had an inflammatory component (Table 1).

Surprisingly, triple-negative breast cancer patients had an excellent initial response to neoadjuvant chemotherapy. Among the 20 patients who had received induction chemotherapy (Table 2), six (42.9%) had a complete response and six (42.9%) had a partial response to treatment. None of them progressed on neoadjuvant chemotherapy (Table 3). Adjuvant therapy was administered to 96% of patients, among whom a taxane-based regimen was used in 38% and a first-line taxane-based regimen was used in 50% (Table 2). Paradoxically, adjuvant hormonal therapy was proposed to the third of patients with breast cancer negative for hormonal markers, with tamoxifen being the most frequently used drug (Table 2). After a median follow-up of 17 months (confidence interval, 1–116 months), 43 patients (25.3%) had relapsed. The risk for recurrence peaked at 1.5 years and becomes almost nil after 3 years. The most common sites of relapse were the brain (19%), lungs (19%), and bones (12%) (Table 1).

The 5-year disease-free survival rate was 75% for stage I, 58% for stage II, and 40% for stage III patients, whereas the 5-year overall survival rate was 88% for stage I, 72% for stage II, and 63% for stage III patients. The median survival time for stage IV patients was 19 months, with a first-line taxane-based regimen used in 50% of cases.

Discussion

The proportion of triple-negative breast cancer patients was evaluated to 9.3% in our study, compared with a proportion of 10%–17% in worldwide studies [4].

The difference between the mean age at diagnosis of triple-negative breast cancer was not significant between our study and international studies (52 years versus 50 years), whereas the mean age at diagnosis of breast cancer, independent of phenotype, was 52 years in Lebanon versus 63 years in the U.S. [11–13].

No statistical difference was found regarding the presence of an inflammatory component between triple-negative breast cancers and other subtypes of breast cancer in Lebanon (10% versus 10%), whereas a positive family history was found in 10% of patients with triple-negative breast cancer compared with 1% of patients with breast cancer when all phenotypes are included [14].

If we compare the staging of triple-negative breast cancer as found in our study with the staging of breast cancer of all phenotypes in Lebanon (stage I, 17% versus 14.4%; stage II, 47% versus 59.9%; stage III, 24% versus 20%; stage IV, 12%

Table 1. Patients characteristics

Variable	*n* of patients	Percentage
Age at diagnosis[a]		
≤35 yrs	13	7.6%
36–49 yrs	69	40.6%
≥50 yrs	88	**51.8%**
Family history[a]		
Positive	15	**9.1%**
Negative	150	90.9%
Degree of relationship		
First (mother, daughter)	1	5.6%
Second (grandmother, granddaughter)	7	38.9%
Third (aunt, niece)	5	27.8%
Second and third	1	5.6%
Unknown	1	5.6%
Tumor histology[a]		
In situ	4	**2.4%**
Invasive	138	83.1%
In situ and invasive	24	14.5%
Invasive[a]		
Invasive ductal carcinoma	136	**81.9%**
Invasive lobular carcinoma	8	4.8%
Mucinous tumor	2	1.2%
Medullary tumor	6	3.6%
Ductal and medullary carcinoma	2	1.2%
Epidermoid tumor	1	0.6%
Ductal and mucinous carcinoma	2	1.2%
Apocrine carcinoma	1	0.6%
Medullary carcinoma and metaplasic tumor	2	1.2%
Ductal carcinoma and epidermoid tumor	1	0.6%
Ductal and lobular carcinoma	1	0.6%
Tumor grade[a]		
I	7	4.64%
II	49	32.45%
III	95	**62.91%**
Ki-67[a]		
Not done	120	79.5%
Done	31	20.5%
Mean	**49.38%**	
Size at time of diagnosis[a]		
<2 cm	48	29.1%
2–5 cm	82	**49.7%**
>5 cm	35	21.2%
Inflammatory component[a]		
Yes	18	10.7%
No	150	89.3%
Extension to chest wall[a]		
Yes	2	1.2%
No	165	98.8%
Positive lymph nodes at time of diagnosis[a]		
Yes	83	**50.3%**
No	82	49.7%
Metastasis at time of diagnosis[a]		
Yes	21	13%
No	141	87%
Location of metastasis[a]		
Bones	6	**25%**
Liver	3	12.5%
Lungs	3	12.5%
Bones and liver	2	8.3%
Bones and lungs	5	20.8%
Lungs and ovaries	1	4.2%
Liver and lungs	1	4.2%

[a]The sum of the numbers of patients isn't always equal to 170 because some of the information was missing in the charts.

Half of the triple-negative breast cancers occurred before the age of 50 years. A positive family history was only found in 9.1% of cases. In situ triple-negative breast tumors were present in 2.4% of patients. The majority of invasive triple-negative breast tumors were of the invasive ductal carcinoma subtype, poorly differentiated, and had a high mitotic index. Approximately half of the tumors were T2 lesions, whereas T4 lesions were present in 11.9% of cases. More than half of the patients were node positive at diagnosis and only 13% were positive for distant metastasis. The most frequent site of metastasis was bone.

versus 5.7%), we can see that triple-negative breast cancer is more often locally advanced at diagnosis [11, 12].

No statistical difference was found between the grade of triple-negative breast cancer in our study and the grade of triple-negative breast cancer in the U.S. (grade III, 63% versus 66%) [3]. As well, no difference was found between the two studies for the Ki-67 proliferation index (~50%) [3], the presence of positive lymph nodes (50% versus 50%) [3], or the sites of metastasis, which were, in order of frequency, the lungs, brain, and liver [8].

Table 2. Treatment

Variable	*n* of patients	Percentage
Neoadjuvant chemotherapy[a]		
Yes	20	11.8%
No	149	88.2%
Type of neoadjuvant chemotherapy[a]		
AT	6	**31.6%**
TAC	6	**31.6%**
AC	2	10.5%
FAC	1	5.3%
TAC and other	1	5.3%
Other	3	15.8%
Surgery[a]		
Quadrantectomy	55	33.0%
Modified radical mastectomy	103	61.6%
Not done	9	5.4%
Adjuvant chemotherapy[a]		
Yes	138	93.2%
No	10	6.8 %
Type of adjuvant chemotherapy[a]		
CMF	7	5.7%
AT	8	6.5%
TAC	25	20.3%
AC	11	8.9%
FAC	44	35.8%
Other	11	8.9%
FAC and other	9	7.3%
TAC and other	3	2.4%
AC and FAC	2	1.6%
CMF and other	2	1.6%
AT and other	1	0.8%
Adjuvant hormonal treatment[a]		
Yes	42	**33.1%**
No	85	66.9%
Nature of adjuvant hormonal treatment[a]		
Tamoxifen	29	72.5%
Exemestane	1	2.5%
Letrozole	3	7.5%
Tamoxifen and Femara	5	12.5%
Tamoxifen and letrozole	1	2.5%
Letrozole and exemestane	1	2.5%

[a]The sum of the numbers of patients isn't always equal to 170 because some of the information was missing in the charts. Paradoxically, one third of patients with negative markers received adjuvant hormonal therapy, with tamoxifen being the most frequently used molecule. Most of the patients underwent modified radical mastectomy. Surgery was almost always combined with either adjuvant or neoadjuvant chemotherapy and eventual radiation therapy. Taxane-based regimens were the most frequently used.
Abbreviations: AC, doxorubicin and cyclophosphamide; AT, doxorubicin and docetaxel; CMF, cyclophosphamide, methotrexate, and 5-fluorouracil; FAC, 5-fluorouracil, doxorubicin, and cyclophosphamide; TAC, docetaxel, doxorubicin, and cyclophosphamide.

Table 3. Response to neoadjuvant chemotherapy

Response	Absolute *n*	Percentage
Complete disappearance of tumor	6	**42.9%**
Decrease in volume >30%	6	**42.9%**
No change in tumor size	1	7.1%
Increase in tumor size	0	0
Bilateral tumors with disappearance on one side and no change on the other side	1	7.1%

Triple-negative breast cancers responded extremely well to neoadjuvant chemotherapy, with the tumor showing either a complete or a partial response to induction chemotherapy in >90% of cases.

In both our study and Dent's study, the peak of recurrence occurred after 6–18 months [8]. Invasive ductal carcinoma was present in 85% of triple-negative breast cancers, compared with 85% of all breast cancers in Lebanon [14]. It was also noted that in situ triple-negative breast tumors existed in 28 patients, and this was also demonstrated by Finn et al. [15]. Cytokeratins 5/6 and 17, BRCA-1 and BRCA-2, and epidermal growth factor receptor (EGFR) are still not regularly tested for in Lebanon.

Our study revealed that taxane-based chemotherapy regimens were the mostly commonly used: 28% in the adjuvant setting and 50% in the metastatic setting. A good initial response to neoadjuvant chemotherapy was found in our study, which was also demonstrated by Carey et al. [9]. Guan et al. [16] evaluated the overall survival rate at 5 years to be 76.9% and Yuan et al. [17] estimated the global survival rate at 5 years to be 73.7%. In recent work published by Bryan et al. [18], it was postulated that triple-negative ductal carcinoma in situ lesions could represent a precursor lesion to invasive basal-like carcinomas. In our database, four patients had triple-negative ductal carcinoma in situ on IHC. They were not included in the analysis. No other survival or disease free survival were found in the literature.

Conclusion

The incidence of triple-negative breast cancer in Lebanon is similar to that described in the literature. More research should be done to assess whether triple-negative breast cancer cases differ demographically and clinically from cases with other subtypes. In order to determine targets for future therapeutic options, it is essential to understand the biology of this particular breast cancer subtype.

The Lebanese Cancer Registry is helping in understanding the epidemiology of breast cancers, and an ongoing case–control study at our institution is aiming to compare the incidence, characteristics, and survival outcomes of patients with different phenotypes of breast cancer [17–22]. International trials are currently studying targeted adjuvant

therapies worldwide, in particular, the use of anti-EGFR and anti–vascular endothelial growth factor receptor therapies in both the neoadjuvant and metastatic settings.

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